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Pesticides and Neurologic Symptoms

We read with interest the recent study titled "Neurologic Symptoms in Licensed Private Pesticide Applicators in the Agricultural Health Study" (Kamel et al. 2005). Although this was a hypothesis-generating study, the authors speculated regarding moderate exposure and associations with neurologic symptoms. Substantiation of hypotheses requires meaningful metrics of exposure and effect, and depends on exclusion and analysis of competing hypotheses for the observations. In our opinion, the article by Kamel et al. falls seriously short in several regards and requires additional data in order to provide credible and defensible conclusions.

Kamel et al. (2005) analyzed a number of symptoms in those "ever" experiencing one of 23 self-reported symptoms in the preceding 12 months. The biologic significance of the outcome "symptom count" is unknown; also, "multiple symptoms" is not a definable disease or illness. The fact that private applicators report headache, nausea, and fatigue does not establish that each is of neurologic origin, particularly given the physical requirements of farming. Indeed, results of the questions used by Kamel et al. (2005) have been shown to agree poorly with objective tests of neurologic function (Lundberg et al. 1997). Further, Kamel et al. limited the analyses to a single episode rather than symptoms that were reported more than once per year (Kamel et al. (2005); Table 2). As a cross-sectional analysis, the data do not permit assessment of the temporal relationship between exposure and symptom onset, and no consideration was given to the transient nature of the reported symptoms. Thus, although the nature of the analysis implies some sort of persistent neurologic condition underlying the reporting of symptoms, no such condition can be established from intermittent symptoms of indeterminate etiology.

In addition to other potential causes for these symptoms, researchers have warned about the role of psychosocial factors in the reporting of non-specific symptoms. According to Spurgeon et al. (1996),

> Many occupational and environmental health hazards present as an increased reporting of non-specific symptoms such as headache, backache, eye and respiratory irritation, tiredness, memory problems, and poor concentration. The pattern and number of such symptoms is surprisingly constant from hazard to hazard suggesting that common psychological and social factors, not directly related to the exposure may be involved.

The role of these factors has been well documented in the psychological literature. Such factors include attitudes and belief systems; current or preexisting stress; workers' perception of the competence and credibility of management; and involvement of the media, pressure groups, and the legal system (Spurgeon et al. 1997). Further, "[p]revention and control strategies are unlikely to be successful if the real sources of the problems are not correctly identified" (Spurgeon et al. 1997).

Because Kamel et al. (2005) relied on self-reported days of application to infer exposure rather than actual measured dose, their assumption of sufficient exposure to cause a biologic effect has severe limitations. The Agricultural Health Study (AHS) has used lifetime exposure days for specific, individual pesticides in other publications (Alavanja et al. 2003, 2004; Engel et al. 2005), but Kamel et al. (2005) offered no support for their change in approach and the validity of a class-wide, rather than pesticide-specific biologic effect. Furthermore, studies indicate that farmers have much less pesticide exposure than is often assumed from self-reported use and even within this low range; the exposure is variable for a given day. For example, in a study of organophosphate applicators, Stokes et al. (1995) identified differences in urinary metabolite levels based on the number of tanks loaded, acres sprayed, and hours sprayed. Other biomonitoring studies have identified a large range of exposure for different pesticides, including applicators with no detectable exposure (Arbuckle et al. 2002; Mandel et al. 2005). The exposure metric used by Kamel et al. (2005) of cumulative lifetime days applied most likely overestimates exposur, in light of these exposure studies of farmer applicators.

We believe that the findings of Kamel et al. (2005) may well be the result of evaluating multiple pesticides as groups at a time in conjunction with other physical or emotional stress related to farming or even a common ailment such as influenza (Dunn et al. 1995). In any event, the conclusions are not justified by the data because there is no coherent disease outcome and no meaningful exposure metric. It is our view that even hypotheses generated by such non-specific data do not meet the stated AHS objective, which is to "provide information that agricultural workers can use in making decisions about their health and the health of their families" (AHS 2005).

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References

Agricultural Health Study. 2005. Homepage. Available: http://www.aghealth.org [accessed 1 November 2005].

Alavanja MCR, Dosemeci M, Samanic C, Lubin J, Lynch CF, Knott C, et al. 2004. Pesticides and lung cancer risk in the Agricultural Health Study cohort. Am J Epidemiol 160:876–885.

Alavanja MCR, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, et al. 2003. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epidemiol 157:800–114.

Arbuckle TE, Burnett R, Cole D, Teschke K, Dosemeci M, Bancej C, et al. 2002. Predictors of herbicide exposure in farm applicators. Int Arch Occup Environ Health 75:406–414.

Dunn JT, Lees-Haley PR, Brown, RS, Williams CW, English LT. 1995. Neurotoxic complaint base rates of personal injury claimants: implications for neuropsychological assessment. J Clin Psychol 51:577–584.

Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, et al. 2005. Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. Am J Epidemiol 161:121–135.

Kamel F, Engel LS, Gladen BC, Hoppin JA, Alavanja MCR, Sandler DP. 2005. Neurologic symptoms in licensed private pesticide applicators in the Agricultural Health Study. Environ Health Perspect 113:877–882; doi:10.1289/ehp.7645 [Online 15 April 2005].

Lundberg I, Hogberg M, Michelsen H, Nise G, Hogstedt C. 1997. Evaluation of the Q16 questionnaire on neurotoxic symptoms and a review of its use. Occup Environ Med 54:343–350.

Mandel JS, Alexander BH, Baker BA, Acquavella JF, Chapman P, Honeycutt R. 2005. Biomonitoring for farm families in the Farm Family Exposure Study. Scand J Work Environ Health 31(suppl 1):98–104.

Spurgeon A, Gompertz D, Harrington JM. 1996. Modifiers of non-specific symptoms in occupational and environmental syndromes. Occup Environ Med 53:361–366.

Spurgeon A, Gompertz D, Harrington JM. 1997. Non-specific symptoms in response to hazard exposure in the workplace. J Psychosom Res 43:43–49.

Stokes L, Stark A, Marshall E, Narang A 1995. Neurotoxicity among pesticide applicators exposed to organophosphates. Occup Environ Med 52:648–653.

Pesticides and Neurologic Symptoms: Kamel et al. Respond

Burns and Goldstein raise several issues regarding our paper (Kamel et al. 2005), in which we reported that applicators chronically exposed to moderate levels of pesticide experience more neurologic symptoms. They assert that our measures of exposure and effect are not "meaningful." We disagree.

Burns and Goldstein state that "'multiple symptoms' is not a definable disease or illness." Although this is true, symptoms cause many medical visits and so are significant to public health. Further, we made no claim that applicators reporting more symptoms had a particular disease. Indeed, in some of our analyses we purposely excluded

individuals reporting neurologic disease in order to evaluate associations of pesticide use specifically with symptoms. We studied a mixed group of symptoms, all sometimes associated with neurologic dysfunction or disease, although with varying specificity. Excluding two relatively nonspecific symptoms (headache and fatigue) did not appreciably change the distribution of the symptom variable. The assertion that we limited our analysis to "a single episode" is inaccurate: our main analyses evaluated multiple rather than single symptoms, and we took symptom frequency into account in our analysis of individual symptoms (Kamel et al. 2005; Table 4). We acknowledged the limitations of cross-sectional analysis in our article. However, the associations we observed were with cumulative pesticide use; accounting for recent use did not change results.

The issue is not whether the symptoms we studied are diagnostic of neurologic or other disease, but whether experiencing these symptoms is associated with pesticide exposure. Burns and Goldstein cite Lundberg et al. (1997) but omit Lundberg et al.'s conclusion that the exposure-related relationship of symptom reporting to organic solvent exposure makes this approach useful for comparing groups with different exposures. At least 23 previous studies used symptom reporting to evaluate neurologic effects of pesticide exposure, with 19 reporting positive associations (Kamel and Hoppin 2004). We extended this approach to a very large group of applicators who had detailed exposure information available.

Burns and Goldstein discuss potential factors related to symptoms, citing Spurgeon's biopsychosocial model (Spurgeon et al. 1996). We agree that personal and social factors likely influence both experience and reporting of symptoms. However, Spurgeon (2002) noted that

> Discussion of the determinants of symptom reporting does not constitute a dismissal of the farmer's illness but simply a recognition that it is likely to result from a complex interaction of physical, psychological, and social processes.

She described a study of farmers whose symptoms were associated with five factors, one being handling sheep within 48 hr of pesticide dipping. Thus, pesticide exposure may still be associated with increased symptoms even (or perhaps especially) when psychosocial factors are taken into account. Most of the factors Burns and Goldstein list are unlikely to be related to exposure in licensed applicators and so cannot explain the associations seen. Further, confounding by psychosocial factors would likely produce associations with all types of pesticides, but our findings were specific to insecticides. Finally, we do not understand Burn's and Goldstein's comment that our findings are "the result … of a common ailment such as influenza"; are they suggesting that pesticide exposure is associated with increased risk of flu?

Burns and Goldstein call our exposure measures limited, citing biomonitoring studies which show that variations in internal exposure are not completely correlated with external exposure. This point is largely irrelevant because the associations seen depend not on identifying the absolute level of pesticide exposure but rather on ranking applicators as relatively more or less exposed. Variation in the degree to which self-reported days of use represents internal exposure is probably nondifferential with respect to symptom reporting, with resulting misclassification likely to bias associations towards the null; the true relationship may be stronger than we observed. Our findings of associations with insecticides only, and with cumulative but not recent exposure, suggest that recall bias does not fully account for our results. We see no problem in combining pesticides for a class-wide analysis, particularly because many grouped pesticides exert effects through similar or related biologic mechanisms. Using class-wide analyses may minimize confounding because most applicators used multiple pesticides. Ultimately, it will be interesting to evaluate the effects of individual chemicals; we are planning such studies.

Thus, our measures of both exposure and effect are sufficient for their purpose, which is to examine the association of symptom reporting with moderate insecticide exposure. Our study clearly demonstrates such an association. Importantly, it is independent of both recent exposure and a history of high exposure or poisoning, suggesting that lifetime exposure at moderate levels may have health consequences. This finding has implications for farmers' health and deserves to be reported and evaluated further.

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References

Kamel F, Engel LS, Gladen BC, Hoppin JA, Alavanja MCR, Sandler DP. 2005. Neurologic symptoms in licensed private pesticide applicators in the Agricultural Health Study. Environ Health Perspect 113:877–882.

Kamel F, Hoppin JA. 2004. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect 112:950–958.

Lundberg I, Hogberg M, Michelsen H, Nise G, Hogstedt C. 1997. Evaluation of the Q16 questionnaire on neurotoxic symptoms and a review of its use. Occup Environ Medicine 54:343–350.

Spurgeon A. 2002. Models of unexplained symptoms associated with occupational and environmental exposures. Environ Health Perspect 110(suppl 4):601–605.

Spurgeon A, Gompertz D, Harrington JM. 1996. Modifiers of non-specific symptoms in occupational and environmental syndromes. Occup Environ Med 53:361–366.

Tungsten Alloy and Cancer in Rats: Link to Childhood Leukemia?

We read with interest the article by Kalinich et al. (2005) on the generation of rhabdomyosarcomas from "embedded weapons-grade tungsten alloy." Although the study design and the reported findings are of great interest, we are concerned about certain statements made in both the "Introduction" and the "Discussion" of the article. In these sections the authors make reference to the allegation that "several cancer clusters in the United States are associated with elevated levels of tungsten in the environment" (Kalinich et al. 2005) Although they accurately point out that "no definitive link … has been established," they suggest that the cancer clusters are part of "a growing list of health concerns related to tungsten exposure." However, the conditions at Fallon, Nevada, and the investigations into a purported link between naturally occurring tungsten and childhood leukemia are very different from the experimental conditions that exist in the implantation study by Kalinich et al. (2005).

The Centers for Disease Control and Prevention (CDC) conducted a thorough investigation into the Fallon cancer cluster; in fact, it was the largest cancer cluster investigation ever undertaken in the United States. The scientists from the CDC and state health departments concluded that exposure to tungsten was not associated with the incidence of childhood leukemia in Fallon (CDC 2003). The genesis of the leukemia cases is still an area of interest and speculation as shown by a recent letter in *EHP* (Daughton 2005). Because Kalinich et al. (2005) inferred

that tungsten somehow played a role in the Fallon leukemias while presenting data suggesting that implanted tungsten alloy caused metastatic tumor formation, readers may confuse the issues and assume that somehow the two effects (rhabdomyosarcoma and childhood leukemia) are related.

We are not questioning the quality of the work presented by Kalinich et al. (2005) or their finding that implanted pellets of a specific combination of tungsten/nickel/cobalt alloy caused an apparent increase in rhabdomyosarcoma with subsequent metastasis to the lung. Rather, we recommend that the authors remain focused on this finding. Suggesting that these results can be linked to, or somehow shed light on, childhood leukemia and exposure to environmental tungsten is both inappropriate and misleading.

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References

CDC. 2003. Cross-Sectional Exposure Assessment of Environmental Contaminants in Churchill County, Nevada. Final Report. Atlanta, GA:Centers for Disease Control and Prevention. Available: http://www.cdc.gov/nceh/clusters/Fallon/study.htm [accessed 2 November 2005].

Daughton CG. 2005. Overlooked in Fallon? [Letter]. Environ Health Perspect 113:A224–A225.

Kalinich JF, Edmond CA, Dalton TK, Mog SR, Coleman GD, Kordell JE, et al. 2005. Embedded weapons-grade tungsten alloy shrapnel rapidly induces metastatic high-grade rhabdomyosarcomas in F344 rats. Environ Health Perspect 113:729–734.

Tungsten Alloy and Cancer in Rats: Kalinich Responds

We would like to address Schell's comments about our article published in *EHP* (Kalinich et al. 2005). Schell expresses concern about certain statements we made in our article about embedded tungsten alloy fragments, especially our reference to the undisputed Centers for Disease Control and Prevention (CDC) finding that there is an increased incidence of childhood leukemia in areas where there are high levels of environmental tungsten (CDC 2003; Sheppard and Witten 2004). Schell contends that our results showing the carcinogenic potential of embedded tungsten alloy fragments have no bearing on the situation in Fallon, Nevada, and believes that our mentioning them "is both inappropriate and misleading." We respectfully disagree.

In our article (Kalinich et al. 2005) we report an unexpected response in rats to tungsten alloys that could not have been predicted by looking at tungsten toxicity alone. We suggested that our results support the advisability for further consideration of tungsten compounds or synergistic effects of tungsten with other environmental factors in cases such as Fallon. We cited several reports in support of such a view. Miller et al. (2001, 2002) indicated that the presence of tungsten in an *in vitro* model system increased the toxicity of both nickel and cobalt in a synergistic manner. Wei et al. (1985, 1987) reported that tungsten exhibited a promoting effect on *N*-nitroso-*N*-methylurea–induced mammary carcinogenesis in rats. Other investigators have also suggested the cause for the Fallon cancer cluster might be an as yet uninvestigated factor or the result of simultaneous or sequential exposure to one or more agents (Daughton 2005).

At this time it is not clear whether these similar findings from diverse research are an unrelated coincidence or whether they suggest a toxicologic property of tungsten not yet understood. What is clear, however, is the need for further research in this area, not only a toxicologic assessment of tungsten alone but also potential synergistic interactions with known toxic agents. The currently proposed National Toxicology Program study of tungsten is an important first step in resolving these issues.

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References

CDC. 2003. Cross-Sectional Exposure Assessment of Environmental Contaminants in Churchill County, Nevada. Final Report. Atlanta, GA:Centers for Disease Control and Prevention. Available: http://www.cdc.gov/nceh/clusters/Fallon/study.htm [accessed 2 November 2005].

Daughton CG. 2005. Overlooked in Fallon? [Letter]. Environ Health Perspect 113:A224–A225.

Kalinich JF, Emond CA, Dalton TK, Mog SR, Coleman GD, Kordell JE, et al. 2005. Embedded weapons-grade tungsten alloy shrapnel rapidly induces metastatic high-grade rhabdomyosarcomas in F344 rats. Environ Health Perspect 113:729–734.

Miller AC, Mog S, McKinney L, Luo L, Allen J, Xu J, et al. 2001. Neoplastic transformation of human osteoblast cells to the tumorigenic phenotype by heavy-metal tungsten-alloy metals: induction of genotoxic effects. Carcinogenesis 22:115–125.

Miller AC, Xu J, Prasanna PGS, Page N. 2002. Potential late health effects of the heavy metals, depleted uranium and tungsten, used in armor piercing munitions: comparison of neoplastic transformation and genotoxicity using the known carcinogen nickel. Mil Med 167:120–122.

Sheppard PR, Witten ML. 2004. Heavy metal content in airborne dust of childhood leukemia cluster areas: even small towns have air pollutants [Abstract]. Eos Trans American Geophysical Union 85: Fall meeting suppl., abstract A11A-0025. Available: http://www.agu.org/cgi-bin/SFgate/SFgate?&listenv=table&multiple=1&range=1&directget=1&application=fm04&database=%2Fdata%2Fepubs%2Fwais%2Findexes%2Ffm04%2Ffm04&maxhits=200&=%22A11A-0025%22 [accessed 4 November 2005].

Wei HJ, Luo XM, Yang SP. 1985. Effects of molybdenum and tungsten on mammary carcinogenesis in SD rats. J Natl Cancer Inst 74:469–473.

Wei HJ, Luo XM, Yang SP. 1987. Effect of molybdenum and tungsten on mammary carcinogenesis in Sprague-Dawley (SD) rats [in Chinese]. Zhonghua Zhong Liu Za Zhi 9:204–207.

Synthetic Musk Compounds and Effects on Human Health?

A recent article by Luckenbach and Epel (2005) on *in vitro* observations of inhibitory properties exhibited by certain nitromusk and polycyclic musk fragrance ingredients on mussel cells raised some concerns regarding potential environmental risks and safety to humans that may be associated with nitromusk and polycyclic musk compounds. The Research Institute for Fragrance Materials would like to address several points that may help readers more clearly understand the meaning and context of the reported research.

The tonnages of musk compounds reported by Luckenbach and Epel (2005) in their article (7,000–8,000 tons) are higher than the industry-reported global tonnage of these materials. From 1995 to 2000, the total worldwide usage declined from 300 tons to 200 tons for musk xylene and musk ketone combined. The 2000 worldwide use of polycyclic musks is approximately 4,000 tons.

Measured concentrations of these compounds in the environment are less than the effects concentrations reported by Luckenbach and Epel (2005). In a review of measured environmental concentrations, Rimkus (1999) stated that the highest reported measurement of hexahydrohexamethyl-cyclopenta (γ)-2-benzopyran (HHCB) in surface water was 12.5 µg/L (0.048 µM). The IC_{50} (concentration that inhibits 50%) reported for polycyclic musks was 2.34 µM. Overall, measured environmental concentrations were 2–6 orders of magnitude lower than the effects concentrations reported by Luckenbach and Epel (2005).

The data reported by Luckenbach and Epel (2005) reflect a method under development. There are many steps between the observation of an *in vitro* effect and effects on whole organisms, ecosystems, and humans. *In vivo* studies in mussels and studies linking mussel gill tissue to undefined tissues in mammals and humans are some of the research necessary to conclude that these higher level effects may exist. These effects would then need to be placed into a risk-based context by comparing them to exposure concentrations.

The safety of nitromusk and polycyclic musk compounds for humans has been extensively tested and affirmed by numerous regulatory agencies and academic scientists around the world [Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) 2002a, 2002b]. The trace environmental levels of the musks continue to be investigated, and environmental safety and monitoring studies are ongoing so that the public can be assured of their safety.

Regarding the environmental effects of synthetic musks, the IC_{10} (concentration that inhibits 10%) values should be compared to no observed effect concentrations (NOECs). The IC_{10} values of the synthetic musks are around the level of the lowest *in vivo* NOECs observed for aquatic organisms.

Table 1 shows that the *in vitro* multixenobiotic resistance (MXR) transporter activity in mussel gill is of the same sensitivity as the effects observed in the standard toxicity tests with aquatic organisms. Thus, at the exposure level where the protective transporter efflux is decreased, rendering the cell more accessible to other potential toxicants, the effects of the synthetic musks are also indicated in other end points, such as development and growth.

The observed effects are not limited to the nitromusk and polycyclic musk compounds.For example, the other chemicals used by Luckenbach and Epel (2005)—verapamil and quinidine—also produced the phenomenon. In the case of verapamil, the IC_{10} was reported at 1–2 orders of magnitude below the nitromusks and polycyclic musks.

I look forward to continued discussions with the Luckenbach and Epel to determine the relevance of the results of this study.

The author is employed by the Research Institute for Fragrance Materials, a nonprofit organization that publishes its work in peer-reviewed literature under the guidance of an independent scientific panel and receives support from the private sector.

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Table 1. Intensity of *in vitro* MXR transporter activity in mussel gill.

	IC10) (mg/L)	Lowest NOEC (mg/L
MK	0.14 mmol = 0.041	0.063
MX	0.09 mmol = 0.027	0.056
AHTN	0.35 mmol = 0.090	0.035
HHCB	0.37 mmol = 0.095	0.068

Abbreviations: MK, musk ketone; MX, musk xylene.

References

Luckenbach T, Epel D. 2005. Nitromusk and polycyclic musk compounds as long-term inhibitors of cellular xenobiotic defense systems mediated by multi-drug transporters. Environ Health Perspect 113:17–24.

Rimkus G. 1999. Polycyclic musk fragrances in the aquatic environment. Toxicol Lett 111:37–56.

SCCNFP. 2002a. Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers Concerning 6-Acetyl-1,1,2,4,4,7-Hexamethyltetraline (AHTN). SCCNFP/0609/02. Available: http://europa.eu.int/comm/health/ph_risk/committees/sccp/documents/out176_en.pdf [accessed 2 November].

SCCNFP. 2002b. Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers Concerning Hexahydro-Hexamethyl-Cyclopenta (γ)-2-Benzopyran (HHCB). SCCNFP/0610/02. Available: http://europa.eu.int/comm/health/ph_risk/committees/sccp/documents/out179_en.pdf [accessed 2 November].

Synthetic Musk Compounds: Luckenbach Responds

In his letter on our recent article in *EHP* (Luckenbach and Epel 2005), Salvito raises important questions about effects of the synthetic musk fragrances regarding *a*) human and environmental health effects, *b*) environmental concentrations of the musks, and *c*) uniqueness of inhibition of efflux transporters to the musks, the effect we described in our article.

a) Regarding health issues, we agree with Salvito that the available evidence indicates minimal direct affects of most synthetic musks on the health of humans and aquatic organisms. However, our data expand the definition of toxicity and detrimental effects to indirect and unanticipated consequences of these chemicals, even if the chemical itself might be nontoxic. The major point of our article (Luckenbach and Epel 2005) was that the musks inhibit efflux (drug) transporters, which act as first lines of defense to pump potentially toxic substances out of cells. These efflux transporters are ubiquitous and are found in bacteria, fungi, plants, and animals, including humans. The transporters have wide substrate specificity, and this binding to many compounds can result in inhibition of activity by competing substrates. As a consequence of transporter inhibition, cells and organisms can therefore become exposed to toxicants normally kept out of their cells.

An unexpected finding was not only that the musks inhibit these transporters in marine mussels but that the effect is long-term and persists up to 24–48 hr after removal of the musk compounds. These indirect and long-term toxicity effects are of particular concern because these chemicals are stable and bioaccumulate; for example, musk xylene has a half-life of 70 days in human tissue (Riedel and Dekant 1999).

Effects on human transporters by the musks cannot be inferred from our results, but they do point to the possibility of an interaction, considering the general property of the transporters to recognize a wide array of substrates. Therefore—and in light of accumulation of the musks in human tissue—research is needed to determine if the musks similarly inhibit the human efflux transporters, thereby compromising this defense against toxicants.

b) The musks are of environmental concern because they enter the water column from incomplete degradation in sewage plants. We agree with Salvito that the reported levels in surface waters are extremely low (picomolar range) but disagree with his conclusion that such levels indicate that musks are not a problem. In spite of these low environmental levels, there is significant bioaccumulation of these chemicals in tissues of mussels and fish, and just several months ago Nakata (2005) reported significant bioaccumulation in cetaceans. The concentrations in aquatic organisms can become quite high, being on the order of nanograms per gram fresh weight, which translates to about 0.1 μM final concentration in tissue (Nakata 2005; Rimkus 1999; Yamagishi et al. 1983).

According to Salvito, worldwide production of synthetic musks are only about one-half of the amount we cite. These lower numbers are even more worrisome because because this means that the potency of the musks to bioaccumulate is even higher.

c) Salvito points out that the inhibition of transporters is not unique to the musks. We agree and note that the observed inhibition of efflux transporter activity by the musks may be the tip of the iceberg. As with the musks, there may be many chemicals that by themselves are not toxic but similarly inhibit the efflux transporters and thereby expose the organism to normally excluded toxicants.

In summary, the available data suggest that efflux transporter inhibition could be a significant indirect, negative, and unappreciated effect of environmental chemicals. Several questions need to be answered: Do these chemicals inhibit human transporters? Are there other anthropogenic and natural products that inhibit these transporters in aquatic organisms and also in humans? Should anthropogenic chemicals be screened for inhibitory activity? If so, should there be voluntary or governmental regulations to ensure that such chemicals do not affect the health of exposed populations through these indirect actions?

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References

Luckenbach T, Epel D. 2005. Nitromusk and polycyclic musk compounds as long-term inhibitors of cellular xenobiotic defense systems mediated by multidrug transporters. Environ Health Perspect 113:17–24.

Nakata H. 2005. Occurrence of synthetic musk fragrances in marine mammals and sharks from Japanese coastal waters. Environ Sci Technol 39(10):3430–3434.

Riedel J, Dekant W. 1999. Biotransformation and toxicokinetics of musk xylene in humans. Toxicol Appl Pharmacol 157(2):145–155.

Rimkus GG. 1999. Polycyclic musk fragrances in the aquatic environment. Toxicol Lett 111(1-2):37–56.

Yamagishi T, Miyazaki T, Horii S, Akiyama K. 1983. Synthetic musk residues in biota and water from Tama River and Tokyo Bay (Japan). Arch Environ Contam Toxicol 12(1):83–89.

Benefits and Risks of Pesticide Testing on Humans

In their review of the history of the U.S. Environmental Protection Agency's (EPA) response to the question of human testing of pesticides, Resnick and Portier (2005) argued that the benefits of such testing outweigh the hazards, and they attempted to refute claims that human testing is both unproductive and unethical. We consider their arguments vague, tendentious, and essentially incorrect.

Unanimously passed by both houses of Congress in 1996, with the support of pesticide manufacturers, pediatricians, and the environmental community, the Food Quality Protection Act (FQPA 1996) added a 10-fold child protective safety factor in choosing a reference dose to two earlier factors, one employed to accommodate the difference between animals and humans and one to accommodate the variance among adults. The single stimulus behind the FQPA was the growing evidence of increased childhood vulnerability, and the single reason for its unanimous, bipartisan passage was to protect children.

The pesticide industry quickly mounted a two-pronged attack on the U.S. EPA's new guidelines and safety factors (U.S. EPA 2000), arguing that children were not more sensitive than adults. At the same time, they launched studies in which organophosphate pesticides were administered to adult " volunteers." This was a palpable effort to circumvent and weaken the 10-fold human/animal safety factor, and it flouted the intent of the law to stimulate the generation of data on the developmental and pediatric toxicity of pesticides. Resnik and Portier (2005), in a curious shift of responsibility, indict the FQPA as a factor in stimulating human studies with their claim that

> A law that was intended to provide additional safety protection for children had the unintended effect of encouraging some companies to test toxic compounds on human beings to avoid the regulatory impact of the law.

With few exceptions the U.S. EPA has failed to use the mandated 10X factor. In June 2002 the U.S. EPA issued its cumulative assessment of the organophosphate pesticides (OPs), determining that for the 30 OPs reviewed, a 1X safety factor (that is, no factor) was used for three OPs and one metabolite, and a 3X reduction was used for the others (U.S. EPA 2002). At no time was a 10X factor used, despite the fact that the U.S. EPA possessed developmental neurotoxicity data for only 6 of the 30 OPs at the time of its assessment

In 1998 the U.S. EPA convened a special committee consisting of members of the Science Advisory Board, the Science Advisory Panel for pesticides, and outside ethicists to examine the ethics of human testing. The committee had two meetings separated by 12 months, and after five drafts, adopted a report that accepted human testing subject to rigorous or severe limitations (U.S. EPA 2000). The two pediatricians on the committee (H.L.N. and R.R.) filed a minority report that became part of the record because we objected to procedural and scientific solecisms. Resnik and Portier (2005) did not mention this report, even though Portier was a member of that committee.

Resnik and Portier (2005) recognize that past industry studies are scientifically unacceptable. They directed their comments to future, yet-to-be-specified studies. Such studies, they stated, "can be conducted only if they meet strict scientific and ethical standards and provide public health or environmental benefits." Resnik and Portier (2005) also stated that studies of adult volunteers "could yield knowledge about the toxic effects on humans, which could promote human health" (National Research Council 2004). The reader is left to wonder what toxic effects would be better understood through human studies, or what health benefits could accrue from short-term volunteer studies. Resnik and Portier (2005) mentioned neither children's health nor developmental toxicity. Instead they proffered the dubious hope that studies could result in stricter safety standards or new legislation that could result in reduced pesticide exposure. In today's regulatory climate, this must be considered a slim possibility. Once more the future standards and laws remain unspecified.

Two major issues in human testing are the relevance of data obtained from adult exposure to risk estimates for children, and the scientific validity of short-term human studies as predictors of health outcomes such as neurodevelopmental deficits and carcinogenesis. It is axiomatic that a study that is poorly designed and cannot produce valid conclusions is unethical on this ground alone.

The provenance of the FQPA (1996) emerged from the growing realization that children are vastly different from adults and that the developing organism, while it is laying down and pruning back neural connections, is much more sensitive to neurotoxicants than fully formed organisms. What could possibly be learned about the risk to this group from studying the effects of toxicants on adults? Resnik and Portier (2005) did not attempt to address this question, but the answer is, very little.

One of the critical issues in evaluating the scientific validity of a study design is statistical power. On this basis alone human studies have failed. A study with inadequate power to find an effect is by definition unethical. This type of study submits subjects to some risk while providing no scientific information. There are roughly 19 million children in the United States ≤ 5 years of age. If a toxicant harmed 1 child in 1,000, that would place 19,000 children at risk nationwide. A study with adequate power to detect an increase in deficit from 1% to 2% would require 3,017 subjects in each group to yield a power of 0.8, at $\alpha = 0.05$. Past industry studies with sample sizes < 50 had about a 3% chance of finding an effect if it were present. No mention of this power finding was made by Resnik and Portier (2005), although this was published by the U.S. EPA Science Advisory Board/Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Science Advisory Panel (U.S. EPA 2000) on which Portier served as a contributing member.

Resnik and Portier's article (Resnik and Portier 2005), when examined in light of specificity, completeness, and relevance to the health of children, fails on all points. It asks the reader to accept unspecified studies on adults as productive of unspecified benefits to human health. The principal toxic target, the health of children, remains unspoken and out of awareness.

J.S is employed by environmental nonprofit organizations with an interest in ensuring that regulations of toxic chemicals are as health-protective as feasible. The remaining authors declare they have no competing financial interests.

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References

FQPA. 1996. Food Quality Protection Act of 1996. Public Law 104-170.

National Research Council. 2004. Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues. Washington, DC:National Academy Press.

Resnick DB, Portier C. 2005. Pesticide testing on human subjects: weighing benefits and risks. Environ Health Perspect 113: 813–817.

U.S. EPA. 2000. Comments on the use of data from the testing of human subjects. A Report by the Science Advisory Board and the FIFRA Scientific Advisory Panel. EPA-SAB-EC-00-017 Washington, DC:U.S. Environmental Protection Agency. Available: http://www.epa.gov/science1/pdf/ec0017.pdf [accessed 2 November].

U.S. EPA. 2002. Revised OP Cumulative Risk Assessment. FQPA Safety Factor. Washington, DC:U.S. Environmental Protection Agency. Available: http://www.epa.gov/pesticides/cumulative/rra-op/l_G.pdf [accessed 10 November 2005.

Pesticide Testing on Humans: Resnick and Portier Respond

In their letter, Needleman et al. suggest that our arguments regarding the ethics of human testing of pesticides (Resnik and Portier 2005) are "vague, tendentious, and essentially incorrect." However, they offer no effective sustained arguments in support of this conclusion.

They cite the Food Quality Protection Act (FQPA 1996) and note that this act led pesticide companies to sponsor studies in humans, in part, to avoid an additional 10-fold human safety factor. They then chastise our article for saying effectively the same thing. Their next point focuses on what they view as a U.S. Environmental Protection Agency (EPA) failure to enforce the FQPA for organophosphate pesticides, an issue that has no bearing on the ethical question of human testing of pesticides. They claim that we failed to specify exactly how human studies could benefit society, but we clearly stated in our article (Resnik and Portier 2005) that these studies could promote public health by providing knowledge that may be useful in regulating pesticides. It is the responsibility of the party sponsoring or conducting a human testing study to demonstrate the relevance and utility of the proposed study with regard to human toxicity.

Needleman et al. contend that we have missed an important issue—the relevance of adult testing to children's risk. This argument is not relevant to our article because we focused on human testing of pesticides on adults, not on children. We seriously doubt whether testing pesticides on children, or on other vulnerable populations, could ever be justified on ethical grounds. It is possible that studies of the effects of pesticides on adults could enhance our understanding of how pesticides affect children, but the party(s) sponsoring the study would need to provide some evidence for this supposition. In our article (Resnik and Portier 2005) we argued that there may be some cases where the public health benefits of testing pesticides on adults justify imposing risks on human subjects. We did not argue that one of the benefits of testing pesticides on adults is to improve the health of children, but we acknowledge that some studies might have this potential benefit.

We addressed arguments concerning the statistical power of human studies in our Supplemental Material, which is available online (http://ehp.niehs.nih.gov/members/2005/7720/suppl.pdf). Good statistical design is one of the key principles that must be considered in evaluating the acceptability of human testing, and we acknowledge that some of the disputed pesticide studies have been underpowered. It is surprising to us that Needleman et al. would raise this concern when their key premise is that human testing of pesticides is never ethical. If testing of pesticides is never ethical, then statistical issues, such as sample size, are irrelevant.

Needleman et al. have confused the issues relating to the FQPA, 10X safety factors, and risk assessment with the questions surrounding human testing of pesticides. We wholeheartedly agree that to conduct a clinical study in humans for the sole purpose of keeping a product commercially viable is unethical. They assume that the only reason why anyone would develop and conduct human studies of pesticides is to promote the interests of pesticide manufacturers. Again, we address this issue in our Supplemental Material (http://ehp.niehs.nih.gov/members/2005/7720/suppl.pdf).

We argue that a study that benefits private industry can be ethical, provided that it also offers scientific or social benefits. For example, clinical trials of new drugs benefit pharmaceutical companies, but they also benefit patients, enhance our understanding of human disease, and improve public health.

The authors declare they have no competing financial interests.

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References

FQPA. 1996. Food Quality Protection Act of 1996. Public Law 104-170.

Resnick DB, Portier C. 2005. Pesticide testing on human subjects: weighing benefits and risks. Environ Health Perspect 113: 813–817.

Infant Methemoglobinemia: Causative Factors

That individually and environmentally mediated cofactors function in the development of infant methemoglobinemia (iMHG) is not a new finding. Studies cited by Fewtrell (2004) note these cofactors. In my work on iMHG, using a nested case–control study that was not cited by Fewtrell (2004), I confirmed that cofactors (feeding practices, individual and infant physiology, etc.) played a role in the disease status of populations under study (Zeman 2000; Zeman et al. 2002a).

Cofactor work completed with Ustyogova et al. (2002) indicated that *in vitro* studies examining exposures below and above the maximum contaminant limit for nitrate show impacts to lymphocyte proliferation and cytokine production with shift in immune response from a Th 1 lymphocyte immune status to a Th 2 lymphocyte, indicating possible decreased resistance to pathological states. Could this be another factor in iMHG? Ustyogova et al. (2002) examined healthy adults, but the study raises the issue of the effects of exposure on the developing immune system of infants. The microbial status of drinking water for participants in the case–control study (Bauer et al. 2003), has been evaluated at the bacterial and parasite levels (Bauer et al. 2003, Zeman et al. 2005). Findings indicated that most water was highly contaminated with fecal coliforms (0–1,000/100 mL) and protozoan oocysts (0–84 cysts/L); when the likelihood of contamination was compared to data on whether or not an iMHG case had occurred in the household, no significant relationship was found.

Fewtrell (2004) claimed that no exposure–response data are available, but two articles (Zeman et al. 2002a, 2002b) reporting on the iMHG case–control study and associated exposure assessment to nitrate/nitrite contradict this. In one of these studies (Zeman et al. 2002a), a bivariate fit of nitrate level in well water and nitrite exposure through water and dietary sources (p = 0.0001) validated the exposure assessment methodology. Table 9 of this article illustrates the relationship strength under bivariate test for a variety of risk factors, and Table 11 provides a multivariate analysis showing the most predictive factors for this study population—exposure to drinking water nitrates, breast-feeding duration, and lack of vitamin use (Zeman et al. 2002a). By stratifying these data for bivariate analysis and comparing the calculated nitrite exposure for each child for low to medium (< 0.1 mg/kg/day to ≥ 0.1–1.5 mg/kg/day) and low to high (< 0.1 mg/kg/day to ≥ 1.5 mg/kg/day) exposures, the likelihood (L) and Pearson (P) calculations show a definite gradation in effect and significance in both situations: low to medium (L = 6.574, p = 0.0103; and P = 4.377, p = 0.0364); low to high (L = 20.7474, p = 0.0001; and P = 15.605, p = 0.0001). I agree, however, that no dose–response relationship has been documented comparing calculated exposure to measured blood methemoglobin level at the time of a clinically diagnosed iMHG case. This would be a gold standard that would help us to tease out the causative factors of iMHG and to establish solidly or refute what looks like, to date, the centrality of the role of nitrate exposure in the etiology of iMHG.

The author declares she has no competing financial interests.

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References

Bauer RJ, Vlad M, Sinca A, Moga D, Mirestean I, Zeman CL. 2003. Field methodology for the determination of the prevalence of Giardia cysts and Cryptosporidium oocysts in drinking water and its association to the development of diarrheal disease in the Transylvania Region of Romania. In: Proceedings of the Sixth International Symposium and Exhibition on Environmental Contamination in Central and Eastern Europe (Herndon RC, ed). Tallahassee, FL:Institute for International Cooperative Environmental Research, Florida State University, 233–238.

Fewtrell L. 2004. Drinking-water nitrate, methemoglobinemia, and global burden of disease: a discussion. Environ Health Perspect 112:1371–1374.

Ustyugova IV, Zeman C, Dhanwada K, Beltz LA. 2002. Nitrates/nitrites alter human lymphocyte proliferation and cytokine production. Arch Environ Contam Toxicol 43:270–276.

Zeman CL. 2000. Exposure Assessment Methodology Development in Support of a Pilot Study of the Long-Term Neuropsychological Impact of Methemoglobinemia and High Nitrate Exposure in Infants of Transylvania, Romania, with an added Case Control Study of MGH Risk Factors.. Ann Arbor MI:UMI, Bell & Howell.

Zeman CL, Kross B, Vlad M.2002a. A nested case–control study of methemoglobinemia risk factors in children of Transylvania, Romania, Environ Health Perspect 110:817–822.

Zeman CL, Seuleanul I, Sinca M, Sinca A, Moga D, Vlad M. 2005. Environmental illness may have contributed to the origins of Transylvanian vampire myths. Int J Global Health 3(2):29–39.

Zeman CL, Vlad ML, Kross B. 2002b. Exposure methodology and findings for dietary nitrate exposures in children of Transylvania, Romania. J Expos Anal Environ Epidemiol 12:54–63.

Infant Methemoglobinemia: Fewtrell Responds

In her letter, Zeman seems to be objecting to three points relating my article (Fewtrell 2004): that the role of cofactors is not new, that her articles were not cited, and that exposure–response data are available.

First, in my article (Fewtrell 2004) I did not suggest that the role of cofactors was a novel discovery, as evidenced by the selection of articles I cited noting such factors. Rather, I noted the fact that the role of cofactors often seems to be overlooked in some of the literature.

Second, as stated in the conclusion (Fewtrell 2004), "the study did not set out to review the role of nitrates in the causation of methemoglobinemia" nor, by extension, the role of cofactors; thus the literature citation was selective.

Finally, I assessed the article by Zeman et al. (2002) in the literature review for my study (Fewtrell 2004), but I felt it did not provide useful drinking water (i.e., exposure) data related to the level of methemoglobinemia in infants (i.e., response data); therefore, the article by Zeman et al. (2002) was not cited (although I do consider the new data presented in Zeman's letter to be of interest).

Three points that influenced my decision not to cite the article by Zeman et al. (2002) are worth noting. First, Zeman et al.'s Figure 2 shows an apparent relationship between nitrate level in wells (parts per million) and "nitrate" (this is presumably nitrite, as described in the figure legend and Zeman's letter) exposure in milligrams per kilogram per day. This was reported to have a correlation of 0.71, presumably resulting in a coefficient of determination of 0.50. However, some reported concentrations are remarkably high, exceeding 1,000 ppm nitrate. The reported relationship appears, visually, to be dependent on a few very high value(s) for the claimed correlation, making inference—or application of the functional relationship—within more usual exposure levels inappropriate. The data points within more "usual" elevated exposure ranges (say < 500 ppm) do not appear to exhibit a clear correlation between nitrate concentration (parts per million) in well water and calculated nitrite intake in milligrams per kilogram per day.

Second, this figure simply claims a correlation between a concentration (i.e., nitrate in water, parts per million) and a precurser of the outcome condition (i.e., calculated nitrite intake, milligrams per kilogram per day), not the "outcome" of interest I discussed (Fewtrell 2004). It is unclear how the boiling of water (which may lead to an increase in nitrate concentrations) is accounted for in the relationship presented by Zeman et al. (2002). The relationship is also likely to be location specific, being dependent upon local feeding habits [e.g., level of formula, tea (chi), vegetables, etc., given to the infant].

Third, Zeman et al. (2002) did not provide a detailed explanation of how the dependent variable numerical values in their Figure 2 were derived, making it difficult to assess the quality of this information.

The selection of appropriate studies to include in any global assessment is difficult and will always be contentious. I hope that these observations explain my decision not to cite the article by Zeman et al. (2002).

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References

Fewtrell L. 2004. Drinking-water nitrate, methemoglobinemia, and global burden of disease: a discussion. Environ Health Perspect 112:1371–1374.

Zeman CL, Kross B, Vlad M. 2002. A nested case-control study of methemoglobinemia risk factors in children of Transylvania, Romania. Environ Health Perspect 110:817–822.

Avian Influenza and UV-B Blocked by Biomass Smoke

Washam (2005) described various poultry inoculation strategies being considered for controlling the spread of avian influenza in Southeast Asia and China. Longini et al. (2005) proposed that a future avian influenza A pandemic might be contained at the source by targeted prophylaxis, quarantine, and prevaccination.

Washam (2005) correctly noted that "Asian farmers, though, are running out of options." I propose a new option: Avian influenza might be controlled by a substantial reduction in regional scale biomass smoke in

Southeast Asia that will allow natural solar ultraviolet-B radiation (UV-B) to suppress the virus before infection occurs.

Influenza viruses and various nonpigmented bacteria are killed by UV-B wavelengths in sunlight (Hollaender and Oliphant 1944). Biomass smoke significantly suppresses natural levels of UV-B, and severe smoke pollution reduced UV-B by up to 95% during the burning seasons in Brazil in 1995 (Mims 1996) and 1997 (Mims FM III, White B, unpublished data). Reduced UV-B on 6 days in August 1997 was well correlated (r^2 = 0.83) with an increase in the ratio of nonpigmented bacteria vulnerable to UV-B to pigmented bacteria that are protected from UV-B (Mims and White 1998). Although airborne influenza viruses were not measured, 1997 hospital admission records at Alta Floresta, Brazil, showed that influenza incidence was highest during the burning season (de Castro GC, personal communication).

Human cases of avian influenza in Thailand and Vietnam peaked during the winter burning seasons of 2003 and 2004 (Thailand Ministry of Public Health 2005). Assuming similar optical properties of biomass smoke in Southeast Asia and Brazil, where UV-B and optical depth are highly correlated, optical depth measurements over Thailand and Vietnam by NASA's Terra and Aqua satellites suggest highly suppressed UV-B during these avian influenza outbreaks (Mims FM III, unpublished data).

Human cases of avian influenza in Thailand and Vietnam since December 2003 have peaked during both the rainy season and the burning season. Thus, periods of prolonged cloudiness and severe smoke pollution could play a role in initiating avian and other influenza outbreaks by attenuating the solar UV-B that might otherwise suppress influenza viruses in outdoor air exposed to sunlight. The transmission of avian influenza to people during these periods is enhanced by the fact that poultry raised for human consumption are often kept within several meters of where people live (World Health Organization 2004).

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References

Hollaender A, Oliphant J. 1944. The inactivating effect of monochromatic ultraviolet radiation on influenza virus. J Bacteriol 48:447–454.

Longini IM Jr, Nizam A, Xu S, Ungchusak K, Hanshaoworakul W, Cummings DAT, et al. 2005. Containing pandemic influenza at the source. Science 309:1083–1087.

Mims FM III. 1996. Significant reduction in UV-B caused by smoke from biomass burning in Brazil. Photochem Photobiol 64:123–125.

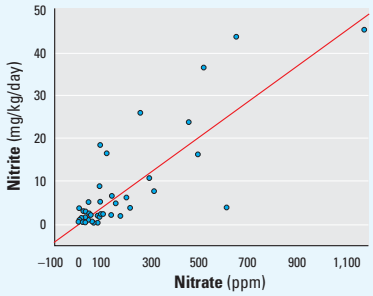
Thailand Ministry of Public Health. 2005. Avian Influenza Surveillance in Human as of July 1, 2005. Available: http://thaigcd.ddc.moph.go.th/AI_case_report_050701.html [accessed 25 August 2005].

Washam C. 2005. On hens and needles. Environ Health Perspect 113:A370.

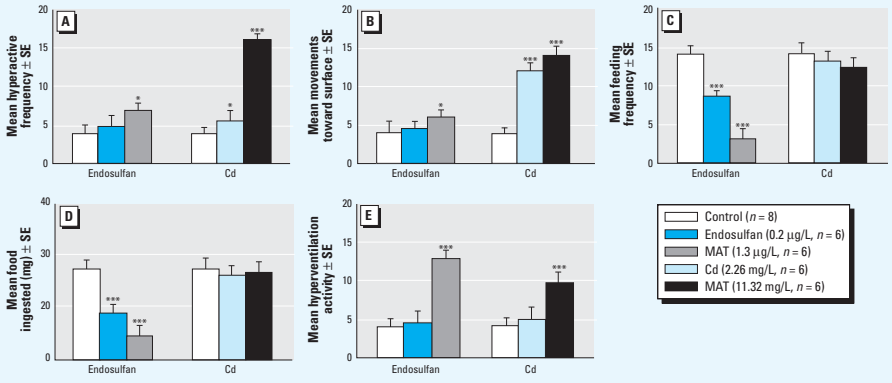
World Health Organization. 2004. Avian Influenza A(H5) in Rural Areas in Asia: Food Safety Considerations. Available: http://www.who.int/foodsafety/micro/avian2/en/ [accessed 25 August 2005].

Errata

There was an error in Figure 2 of Zeman et al. [Environ Health Perspect 110:817–822 (2002)]: the *y*-axis should have been labeled "Nitrite" instead of "Nitrate." The corrected figure appears below.



In Giusi et al. [Environ Health Perspect 113:1522–1529 (2005)], the colors were incorrect in the key to Figure 1. The corrected figure appears below.



EHP regrets the errors.